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| EXAMINER | |
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| BERTOGLIO, VALARIE E | |
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| SHORTENED STATUTORY PERIOD OF RESPONSE | MAIL DATE | DELIVERY MODE |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/731,542 | BEHBOODI ET AL. | |
| | Examiner | Art Unit | |
| | Valarie Bertoglio | 1632 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *11 December 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-20,22-34 and 36-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20,22-34 and 36-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on *N/A* is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

Applicant's reply dated 12/11/2006. Claims 1,11,17,20,22-24 and 29 have been amended. Claims 21 and 35 have been cancelled. Claims 36-39 have been added. Claims 1-20, 22-34 and 36-39 are pending and under consideration in the instant office action.

### *Priority*

The amendment to the specification adding a claim for the benefit of a prior-filed application US Provisional Application No. 60/432,163, filed 12/10/2002 is noted.

### *Claim Objections*

The objection to claim 1 is withdrawn in light of Applicant's amendment to the claim.

The objection to claim 20 is withdrawn in light of Applicant's amendment to claim20.

The objection to claims 21 and 35 is rendered moot by the cancellation of the claims.

### *Claim Rejections - 35 USC § 101*

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The prior rejection of claim 20 is withdrawn. The claim now requires the production of an offspring of a transgenic, non-human mammal. This amendment overcomes the prior rejection of record because the recitation of "transgenic" distinguishes the non-human mammal from a naturally occurring mammal.

***Claim Rejections - 35 USC § 112-1st paragraph***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

*Scope of Enablement*

Claims 1-20 and 22-23 remain rejected and claims 24-34 and 36,38 and 39 are newly rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for 1) a method for cloning a transgenic non-primate mammal through a nuclear transfer process using a non-primate mammalian cell as a source of a donor nucleus to form a first nuclear transfer embryo, said process comprising an additional recloning step using a cell from the first nuclear transfer embryo, and 2) said method wherein it further comprises a step of genetically modifying a fibroblast donor cell in vitro prior to nuclear transfer, does not reasonably provide enablement for 1) the claimed method using a primate species, or 2) a transgenic non-primate mammal wherein the transgene is not expressed, or 3) the claimed method wherein a transgene is introduced to non-fibroblast somatic cells in culture or 4) use of multiple donor cell nuclei for a single recipient oocyte. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 24-34 were previously rejected as lacking enablement for the full breadth of the claims (page 11 of the office action dated 06/06/2006). Applicant has amended claims 24 and 29 to overcome the grounds of rejection necessitating the full lack of enablement. The claims are now included in the instant scope of enablement rejection as necessitated by amendment. Claims 36,38 and 39 are newly added claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening.

However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a prima facie case are discussed below.

Applicant's arguments have been fully considered and are found partially persuasive as set forth below.

1) The aspect of the rejection pertaining to the failure of the specification to enable use of donor cells of any type other than fibroblast is withdrawn as it relates to claims 1-18, 20,22 and 23 in light of Applicant's amendments to the claims. The claims now require use of a transgenic non-human mammal as a donor source and no longer encompass introducing a transgene into a donor cell in culture. The non-enabled embodiment was the transfection of primary cells in culture and their use in subsequent nuclear transfer. The aspect of the rejection no longer applies to these claims as amended.

However, claim 19 and newly added claim 36 requires an additional step of inserting a gene into the donor cell while in culture. Thus, these claims would be drawn to addition of a second transgene as the parent claims now require use of a transgenic non-human mammal. Such a method step is only enabled for fibroblast cells of non-primate mammals as set forth at pages 7-10 of the previous office action dated 06/06/2006..

*Applicant's arguments:* Applicant argues with respect to claim 19 (which also applies to newly added claim 36) that the art quoted by the Examiner as evidencing the underdeveloped nature of transfecting primary cells prior to nuclear transfer, pertains to the generation of generic modifications of somatic cells in culture. Applicant argues that contrary to the Examiner's conclusion, the art of record demonstrates that it is possible to alter somatic cells in culture and that the Examiner has not demonstrated that it would require undue experimentation to alter somatic cells and use them in the claimed method (paragraph bridging pages 10-11 of Applicant's Remarks).

*Response to arguments:* In response, as set forth at pages 7-10 of the previous office action dated 06/06/2006, the state of the art supported the unpredictable and underdeveloped nature of gene targeting in any cell type (see Schnieke, Thomson, Polejaeva & Campbell and Denning, all cited previously). The art has established that it requires a large number of population doublings to obtain recombinant primary cells. For example, Denning (2001, of record) taught that primary cells have limited proliferation capacity and any genetic modifications and nuclear transfer must be accomplished prior to senescence. In a study of sheep and goat primary somatic cells, Denning found that of primary somatic cells, fibroblasts were the only cells that either grew at all from the primary cell source or has sufficient population doublings for the selection required in targeted gene transfer. Sheep primary cell cultures primarily were composed of fibroblasts after the third passage or about 12 doublings (page 224, col. 2, lines 11-13). In a similar analysis of pig primary cultures, fibroblasts, as in the sheep study, became the predominant cell-type after three passages, but, unlike sheep, pig fibroblasts underwent a crisis after 40 population doublings and had an unstable karyotype (page 224, col. 2, parag. 4 line 4 to page 225, col. 1, line 8). Denning also states that even if sufficient population doublings could be achieved for selection, many of the pure sheep targeted clones senesced before they could be expanded for nuclear transfer (page 228, col. 1-2, bridg. sent.).

Thus, it is maintained that claims 19 and 36 are not enabled for use of any donor cell type other than fibroblast because the method requires introduction of a transgene into a donor cell after isolation from a donor mammal and prior to introduction into an oocyte.

2) *Applicant's arguments:* With respect to the aspect of the rejection relating to nuclear transfer in primate species (specifically refer to pages 6-7 of the office action dated 06/06/2006), Applicant argues that at the time of filing, cloning of primates was enabled and refers to the success of Meng *et al,* (1997, IDS).

*Response to arguments:* In response, according to Simerly et al., (of record), Meng *et al.* is the only successful cloning of rhesus primates. The cloning by Meng *et al.* was performed with embryonic blastomeres, and has not since been repeated (see Simerly, page 297, col. 1, paragraph 1). Therefore, the teachings of Meng *et al.* are not enabling as those skilled in the art have not been successful in reproducing the results, making primate cloning, at best, highly unpredictable even using embryonic blastomeres rather than somatic cells as encompassed by the claims. No primate cloning using adult somatic cells has been made of record. The specification has not provided the guidance necessary, in light of the art-recognized inability to reproduce the teachings of Meng *et al*, to clone primates or primate embryos.

3) The aspect of the rejection relating to the lack of enablement for the offspring of claim 20 wherein expression of the transgene is not required (page 10, last paragraph of the office action dated 06/06/2006) is withdrawn in light of Applicant's amendment to the claim.

The following new grounds of rejection is necessitated by Applicant's amendments to claim 1.

Claim 1 has been amended to recite that the cell nuclei are transferred in to the enucleated oocyte. The specification and the art at the time of filing teaches fusion or injection of a single donor cell or donor

cell nucleus into an enucleated oocyte. The specification provides no guidance with respect to use of multiple donor cells or cell nuclei for each recipient oocyte. The specification and the art at the time of filing do not teach what effect such a procedure would have on an oocyte, however, the presence of 2 or more diploid nuclei in a single oocyte would not likely undergo proper cell cycle events. Thus, one of skill in the art would not know how to carry put the instant invention using multiple donor cells for a single oocyte. Accordingly, the claims should clearly be limited to introduction of a single donor cell into a single oocyte.

*Lack of Enablement*

The rejection of claim 21 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement is rendered moot by Applicant's cancellation of the claim. However, the term "chimeric" is reintroduced in newly added claim 37, necessitating the following new rejection.

In addition to the applicable grounds of rejection under scope of enablement, above, the following lack of enablement rejection is necessitated for the full breadth of the claim.

Claim 37 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. In addition to the above maintained aspects of enablement that apply to claim 37, claim 37 lacks enablement for the entire scope of the claim as set forth below.

Claim 37 is unclear as written (see below), however, it appears the claim is drawn to use of an embryo, produced by nuclear transfer, in making a chimeric animal by combining said embryo with a fertilized embryo (single cell embryo or diploid zygote), such that a resulting progeny would be comprised of two genetically distinct sets of cells. As set forth at page 11 of the office action dated

06/06/2006, chimeras are highly variable because the tissue distribution in a chimera cannot be controlled or be predictably reproduced. Therefore, one of skill in the art would not know how to make any chimera as claimed and would not know how to use the chimera as no two resulting chimeras would be the same.

Because the specification fails to provide any guidance as to combining an embryo with a fertilized embryo and in light of Applicant's of the lack of clarity of the claim, claim 37 also reads on addition of a diploid nucleus to a zygote (fertilized 2n embryo). This would result in a tetraploid (4n) embryo for which the specification provides no use and which is not a chimera as claimed.

The rejection of claims 24-35 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement is withdrawn in light of Applicant's amendment to the claims such that the oocyte is no longer required to be used as a nuclear donor. The claims were included in to the scope of enablement rejection, above.

***Claim Rejections - 35 USC § 112-2nd paragraph***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

*The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.*

Claims 1-20,22-34 remain rejected and newly added claims 36-39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1) The rejection of claim 1 as lacking clarity in formation of transgenic embryos without the introduction of a transgene is withdrawn in light of Applicant's amendment to the claim requiring the donor cell be obtained from a transgenic mammal.

2) The rejection of claim 1 for lacking antecedent basis for "the desired differentiated cell or cell nucleus" in line 8 is withdrawn in light of Applicant's amendment to the claim. However, the claim now

encompasses transfer of multiple cell nuclei to a single recipient oocyte, which is not enabled as set forth above.

3) The rejection of claim 1 for lacking antecedent basis for the term "the cell couplet" in line 10 is withdrawn in light of Applicant's Applicant's amendment to the claim. Applicant has amended the claim to recite formation of a cell couplet in line 9.

4) The rejection of claim 1 as being incomplete for not including method steps requiring live birth is withdrawn. Applicant has amended the preamble. However, it is noted that a fetus is considered to be a mammals.

5) The rejection of claim 1 for having method steps that are not commensurate in scope with the preamble is withdrawn in light of Applicant's amendment to the claim.

6) The rejection of claim 17 as lacking antecedent basis for the term "the fetus" is withdrawn in light of Applicant's amendment to the claim.

7) The rejection of claim 19 as being unclear because it depends from a method of cloning yet results in a genetically distinct mammal is withdrawn as the method of claim 1 is no longer directed to a method of "cloning", per se, and does not require the mammal obtained be identical to any degree, to the donor mammal.

8) The rejection of claims 20,21 and 35 for lacking antecedent basis for the limitation "The resultant offspring" is withdrawn amendment to the claim. Claims 21 and 35 have been cancelled, rendering the rejection moot with respect to these claims.

9) Claims 22 remains rejected as set forth at page 14, paragraph of the office action dated 06/06/2006. The rejection relating to claim 23 is withdrawn in light of Applicant's amendments to the claim as it contains a negative limitation reciting that cytochalasin B is not used at all in the cloning protocol..

While claim 22 no longer lacks antecedent basis for the limitation "the cloning protocol" the claim is drawn to use of cytochalasin B in the method of claim 1. Applicant argues at page 12, paragraph 7, that the claims have been amended to remove the term "cloning protocol". However, it remains unclear which steps of the base claim 1 are to require such use. It could refer to all steps of the claim or just to those directly involving the combination of a nucleus with a cytoplast. The specification teaches use of cytochalasin B for two independent steps, in enucleation of the oocyte and in introduction of the donor nucleus to the cytoplast. The former requires use of cytochalasin B and the latter use is optional (see page 13 of the specification). The art has taught use of cytochalasin B in enucleation (for example see Campbell, 1994) but has taught that in some cases while used in enucleation, it is preferably omitted from steps of introducing the donor nucleus (for example, see Park et al., 1994, IDS). Therefore, for the purpose of examination under 35 USC 102 and 103, see below, because the specification and the art indicate necessity of cytochalasin B in enucleation but not in introduction of donor nucleus, the claims are interpreted to refer to the use of cytochalasin B in the method of claim 1 as it relates to the step of introducing the donor nucleus.

10) The rejection of claims 24 and 29 as requiring use of oocytes as donor cells is withdrawn in light of Applicant's amendments to the claims.

New grounds of rejection necessitated by Applicant's amendments to the claims are presented below.

Claim 1 is unclear because it requires, at step (i), obtaining a single cell as a source of multiple nuclei. It is unclear if the claim is missing a step of expanding said single cell to obtain multiple cells that would provide multiple cell nuclei or if it is intended to refer to obtaining a single cell comprising multiple cell nuclei. Claims 2-19,22-34 and 36-39 depend from claim 1.

Claim 20 is unclear because it requires, at step (i), obtaining a single cell as a source of multiple nuclei. It is unclear if the claim is missing a step of expanding said single cell to obtain multiple cells that would provide multiple cell nuclei or if it is intended to refer to obtaining a single cell comprising multiple cell nuclei.

Claims 19 and 36 are unclear. It is unclear where the desired gene is inserted. It is also unclear what is being inserted (line 2) into the enucleated oocyte. As written, the claims can each be interpreted as modification of a desired gene and insertion of the desired gene into the oocyte. The claim reads on insertion of a desired gene wherein in it is not set forth where the desired gene is inserted, prior to insertion into an enucleated oocyte, wherein it is not set forth what is inserted into the oocyte, i.e. the desired gene, the offspring (claim 36 only), or the donor cell or donor cell nucleus..

Claim 20 is unclear at the last line in stating "that expresses a transgene". It is not clear if the transgene is expressed is the transgene comprises by the donor mammal or some other transgene. Use of the term "a transgene" implies that it can be any transgene, not necessarily the transgene of the donor mammal. While only one transgene appears to be recited in the method steps of this claim, the invention as a whole encompasses insertion of other transgenes into the donor cell (see claim 19 for example). Thus, clarification is necessary.

Claim 37 recites the limitation "said embryo" in lines 1-2. There is insufficient antecedent basis for this limitation in the claim. It is further unclear whether the claim is intended to be directed to adding an embryo to a single cell fertilized oocyte (zygote) or a multicellular, developing embryo. Use of the term "fertilized" renders the terminology "fertilized embryo" unclear in light of the well-known technology of fusing embryonic cells with a developing blastocyst. Furthermore, it is noted that the claim is directed to the offspring of claim 20, which is a product by process claim. Altering the process with the method step of claim 37, may change the product such that it is no longer that of claim 20. Thus, it is wholly unclear what Applicant is intending to claim.

***Claim Rejections - 35 USC § 102***

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

1) The rejection of claims 20 and 35 as being anticipated by Wilmut (1997, IDS) is withdrawn in light of Applicant's amendments to the claim 20. Claim 35 has been cancelled, rendering the rejection moot with respect to this claim. Claim 20 now requires that the donor and resulting offspring be transgenic.

2) Claim 20 remains rejected and newly added claim 37 is rejected under 35 U.S.C. 102(b) as being anticipated by Mansour [1993, of record]. The rejection is maintained and applied to newly added claim 37 for reasons of record set forth at pages 17-18 of the previous office action dated 06/06/2006. The rejection is rendered moot with respect to claim 21 as the claim has been cancelled.

Claim 20 has been amended and is drawn to an offspring made by a recited method of nuclear transfer, rather than depending from the method of claim 1 as previously claimed. The claim is a product by process claim. Claim 37 adds a method step of combining two embryos, one produced by the claimed process in claim 20, to produce a chimera.

Mansour taught a method of making transgenic mice and the resulting transgenic offspring (page 15, col. 2, paragraphs 3-4).

A mammal obtained by the method of claim 20 would not differ structurally from a mammal of the same species obtained through any other method, including natural mating and birth or through traditional transgenic means including introducing a transgene in an ES cell or oocyte. A chimeric mammal obtained by the process of claim 37 does not appear to differ in structure form a chimeric mammal of the same species obtained by any other method, However, it is noted that claim 37 is highly unclear as set forth above. Patentability of a product-by-process claim is determined by the novelty and nonobviousness of the claimed product itself without consideration of the process for making it that is

recited in the claims. See In re Thorpe, 227 USPQ 964 (Fed. Cir. 1985). Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. See In re Ludtke 441 F.2d 660, 169 USPQ 563 (CCPA 1971). Whether the rejection is based on "inherency" under 35 USC 102, on "prima facie obviousness" under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. In re Best, Bolton, and Shaw, 195 USPQ 430, 433 (CCPA 1977) citing In re Brown, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972). Further, see MPEP §2113, "Even though product-by process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process."

Applicant's arguments have been fully considered and are not persuasive. Applicant argues that the Examiner has not met the burden in showing that the claimed product is the same as that of Mansour.

In response, Applicant is reminded, that, where the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. See In re Ludtke 441 F.2d 660, 169 USPQ 563 (CCPA 1971). A cloned transgenic mouse would not differ structurally either from, say its parent obtained by another method or an identical transgenic mouse comprising the same transgene made through a means other than nuclear transfer. Mansour taught chimeric transgenic mice, as well as non-chimeric, transgenic mice. Thus, these products, although made by a different method, produce the products that Applicants instantly claim. Thus, the burden shifts to Applicants with regard to distinguishing the prior art teachings and the

claimed invention. In particular, MPEP §2113 states that, "Once a product appearing to be substantially identical is found and a 35 U.S.C. 102/103 rejection made, the burden shifts to the applicant to show an unobvious difference." In particular, this section states that, "Once the examiner provides a rationale tending to show that the claimed product appears to be the same or similar to that of the prior art, although produced by a different process, the burden shifts to applicant to come forward with evidence establishing an unobvious difference between the claimed product and the prior art product. In re Marosi, 710 F.2d 798, 802, 218 USPQ 289, 292 (Fed. Cir. 1983)." Applicants have not provided any evidence or reasoning to show an unobvious difference between the claimed product and prior art product. Applicant's general assertion that cloning results in a different product has not been substantiated specifically. Thus, this rejection is maintained.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

1) The rejection of claims 1,2,5-9,11,13,17,19, 20 and 22 under 35 U.S.C. 103(a) as being obvious over Schnieke et al. (1997) as evidenced by Wilmut (1997, IDS), by Campbell (1996, IDS) and by Campbell [1994,], in view of Zakhartchenko (1999, IDS) or Wells (1999, IDS) is withdrawn in favor of the following new rejection necessitated by Applicant's amendment to claim 1 requiring that the source of donor cells be a transgenic non-human mammal. Thus, the new rejection is necessitated by amendment.

Claims 1,2,5-9,11,13,17,19,20,22,36, and 39 are rejected under 35 U.S.C. 103(a) as being obvious over Schnieke et al. (1997) as evidenced by Wilmut (1997, IDS), by Campbell (1996, IDS) and by Campbell [1994,], in view of Zakhartchenko (1999, IDS) or Wells (1999, IDS) and further in view of Zakhartchenko (2001, IDS).

Claim 1 is drawn to a method of cloning a non-human mammal comprising transferring the nucleus of a differentiated mammalian cell into an enucleated oocyte of the same species, simultaneously activating the resulting cell couplet, culturing the embryo until it reaches at least the two-cell stage and using a cell from said embryo to form a second embryo through a second round of nuclear transfer. Claim 2 requires that the donor cell be derived from mesoderm. Claims 5 and 6 requires that the donor cell be from fetal tissue or cells and claim 7 requires it be a fibroblast while claim 11 is drawn to additional specific cell types for the donor cell. Claims 8 and 9 are drawn to specific mammalian species. Claim 13 requires in vivo oocyte maturation. Claim 17 requires development of the fetus into an offspring. Claim 19 requires a transgenesis step. Claim 20 is drawn to an offspring made by the claimed method and claim 22 requires use of cytochalasin B in the cloning protocol. Claim 36 is drawn to the offspring of claim 20 wherein the process used to make the offspring requires insertion of a transgene into the donor cell in

culture. Claim 39 is drawn to the offspring of claim 20 wherein the process used to make the offspring requires that the oocyte by matured in vivo.

Schnieke taught cloning of ovine, an ungulate, by nuclear transfer using quiescent fetal fibroblasts, which are differentiated, mesodermally derived cells, (page 2130, col. 3, paragraph 4). Schnieke transformed the fibroblasts with a transgene, which is required by claims 19 and 36. Schneike obtained oocytes from the same species, sheep, incubated them in medium containing cytochalasinB (claim 22) prior to enucleation (taught by reference at Schnieke page 2131, col. 3, paragraph 3 to Campbell, 1994, page 1386, col. 1, paragraph 5 through Campbell, 1996). Donor cells were transferred into the oocyte and fusion and activation were simultaneously induced by electrical shock pulses (taught by reference at page 2131, col. 3, paragraph 3 and Wilmut, page 813, col. 1, paragraph 3). It is noted that Schnieke taught many of the claim limitations by reference to which can be found at page 813 of Wilmut and also, by further reference to Campbell, 1996 that references Campbell, 1994. It is also noted that the oocytes were recovered at metaphase II from the oviducts (see Campbell, 1994, page 1386, col. 1), which are in vivo matured (claims 13 and 39). Schnieke did not teach a re-cloning step as required by step (vii) of claim 1 or use of a transgenic mammal as a source of donor cells.

However, both Zakhartchenko (1999) and Wells (1999) taught growing a first nuclear transfer embryo and using morulae from the first cloning round (see paragraph bridging pages 326-327 of Zakhartchenko and page 998, col. 2, paragraph 4 of Wells). Both Zakhartchenko and Wells each taught increased developmental capacity and cloning efficiency using a recloning step (see Zakhartchenko, page 326, col. 1, paragraph 2 and page 330, col. 1, paragraph 4; see also Wells, page 999, col. 2, paragraph 5).

With respect to the newly added limitation requiring that the donor cell come from a transgenic non-human mammal, Zakhartchenko (2001) taught use of a transgenic calves as a source of differentiated donor cells (page 363, col. 1, paragraph 4). Importantly, Zakhartchenko also taught the caveats associated

with transfection of donor cells in culture, providing motivation to use a known transgenic mammal as a donor rather than attempting to introduce a transgene de novo, to donor cells in vitro.

It would have been obvious for one of skill in the art at the time of filing to combine the teachings of nuclear transfer in cloning a non-human mammal of Schnieke with those of wither Zakhartchenko or Wells, adding a recloning step. One would have been motivated to add a recloning step because both Zakhartchenko and Wells taught that greater efficiency of cloning resulting in live birth occurs when a recloning step is used. It would have been obvious also for one of skill in the art at the time of filing to combine the teachings of nuclear transfer in cloning a non-human mammal of Schnieke, Zakhartchenko (1999) or Wells with those of wither Zakhartchenko (2001), using a transgenic mammal as a source of transgenic donor cells. One would have been motivated use a transgenic mammal because such a mammal would already have the transgene in the genome and characteristics of expression and function of the transgene would be known, avoiding the possibility of having a non-functional transgene in a resulting nuclear transfer mammal following transfection of non-transgenic donor cells in culture. Furthermore, Zakhartchenko taught that transfection of donor cells in culture had adverse effects on cloning efficiency (page 366, col. 2, paragraph 2-page 367). Thus, when available, one of skill in the art would be motivated to use a known, desired transgenic mammal as a source of donor cells rather than transfecting donor cells in culture.

One would have a reasonable expectation of success in combining the above teachings because the techniques necessary for the recloning step were known and are merely repetition of the steps taught by Schnieke. Use of a transgenic mammal as opposed to a non-transgenic mammal does not alter the expectation of success and is further motivation for use of a transgenic mammal as a donor as Zakartchenko (2001) taught the adverse effects of in vitro transfect of donor cells.

Thus, the claimed invention, as a whole, is clearly prima facie obvious in the absence of evidence to the contrary.

Applicant's arguments relating to the rejection of claims 1,2,5-9,11,13,17,19, 20 and 22 under 35 U.S.C. 103(a) as being obvious over Schnieke et al. as evidenced by Wilmut, by Campbell and by Campbell, in view of Zakhartchenko or Wells (see pages 19-21 of the office action dated 06/06/2006) are applicable to the new rejection set forth above.

Applicant argues that the references fail to teach the limitations of part (vi) of claim 1 and also fail to teach the limitation that the desired differentiate mammalian cell is from a transgenic non-human mammal.

In response, both Zakhartchenko (1999) and Wells (1999) taught growing a first nuclear transfer embryo and using morulae from the first cloning round (see paragraph bridging pages 326-327 of Zakhartchenko and page 998, col: 2, paragraph 4 of Wells). Both Zakhartchenko and Wells each taught increased developmental capacity and cloning efficiency using a recloning step (see Zakhartchenko, page 326, col. 1, paragraph 2 and page 330, col. 1, paragraph 4; see also Wells, page 999, col. 2, paragraph 5).

With respect to the newly added limitation requiring that the first donor cell, that in step (i) requiring that the donor cell come from a transgenic non-human mammal, Zakhartchenko (2001) taught use of a transgenic calves as a source of differentiated donor cells as set forth above.

2) The rejection of claims 3,4,10,12,14 and 15 under 35 U.S.C. 103(a) as being unpatentable over Schnieke as evidenced by Wilmut, by Campbell (1996) and by Campbell (1994), in view of Zakhartchenko (1999, IDS) or Wells (1999, IDS) as previously applied to claims 1,2,5-9,11,13,17,19, 20 and 22, and further in view of Campbell (WO 00/42174, published 20 July 2000) is withdrawn in favor of the following rejection, necessitated by the amendment of claim 1.

Claims 3,4,10,12,14, and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schnieke (1997) as evidenced by Wilmut (1997), by Campbell (1996) and by Campbell (1994), in view of Zakhartchenko (1999, IDS) or Wells (1999, IDS) as applied to claims 1,2,5-9,11,13,17,19, 20,22,36 and 39 above, and further in view of Campbell (WO 00/42174, published 20 July 2000) and further in view of Zakhartchenko, (2001, IDS).

As set forth above, Schnieke taught a method of cloning a sheep using fetal fibroblast cells.

Schnieke did not teach using adult cells (claim 10), ectodermally or endodermally derived cells (claims 3 and 4) or the cells from any of the organs listed in claim 12, as a nuclear donor. Schnieke did not teach use of in vitro maturation of oocytes (claim 14) or applying the cloning methods to rodent species as required by claim 15. Schnieke did not teach use of a transgenic mammal as a source of donor cells.

However, Campbell taught using any cell population from any stage in the life of an animal (see page 3, lines 25-29, and page 10, line 20-page 11, line 6). Campbell also taught that oocytes could be matured in vitro (page 13, lines 20-22). Furthermore, Campbell taught applying the methods of cloning to ungulate as well as rodent species (paragraph bridging page 3-4).

With respect to the newly added limitation requiring that the first donor cell, that in step (i) requiring that the donor cell come from a transgenic non-human mammal, Zakhartchenko (2001) taught use of a transgenic calves as a source of differentiated donor cells (page 363, col. 1, paragraph 4). Zakhartchenko also taught the caveats associated with transfection of donor cells in culture, providing motivation to use a known transgenic mammal as a donor rather than attempting to introduce a transgene de novo, to donor cells in vitro.

It would have been obvious at the time of filing to combine the methods of Schnieke and of Zakhartchenko (1999) or Wells and Zakhartchenko (2001) (see above) with the teachings of Campbell using cells derived from an adult mammal to make a cloned mammal by nuclear transfer, including rodent

species using in vitro matured oocytes. One of skill in the art at the time of filing would have been motivated to use a cell derived from an adult mammal to avoid having to generate a fetus as well as to clone an adult, rather than cloning a fetal offspring of a desired adult. Use of a somatic cell to clone an adult would allow for formation of genetically identical tissues that could be use to treat diseases, disorder or injury in a mammal. One of skill in the art would have been motivated to use the claimed methods in rodent species because the method provides a means of introducing transgenes into rodent species that are otherwise not amenable to transgenesis. One of skill in the art would have been motivated to substitute in vitro matured oocytes for in vivo matured oocytes because in vitro maturation would allow for harvesting of large numbers of immature oocytes from an ovary of a pig over hormonally inducing in vivo maturation and release of oocytes from pigs in vivo. In vitro maturation also allows for collection of oocytes post-mortem. Furthermore, one would have been motivated use a transgenic mammal because such a mammal would already have the transgene in the genome and characteristics of expression and function of the transgene would be known, avoiding the possibility of having a non-functional transgene in a resulting nuclear transfer mammal following transfection of non-transgenic donor cells in culture. Furthermore, Zakhartchenko taught that transfection of donor cells in culture had adverse effects on cloning efficiency (page 366, col. 2, paragraph 2-page 367). Thus, when available, one of skill in the art would be motivated to use a known, desired transgenic mammal as a source of donor cells rather than transfecting donor cells in culture.

One would have a reasonable expectation of success in combining the above teachings because use of a transgenic mammal as opposed to a non-transgenic mammal does not alter the expectation of success and is further motivation for use of a transgenic mammal as a donor as Zakartchenko (2001) taught the adverse effects of in vitro transfect of donor cells.

Thus, the claimed invention, as a whole, is clearly prima facie obvious in the absence of evidence to the contrary.

Applicant's arguments relating to the rejection of claims 3,4,10,12,14 and 15 under 35 U.S.C. 103(a) as being obvious over Schnieke et al. as evidenced by Wilmut, by Campbell and by Campbell, in view of Zakhartchenko or Wells and further in view of Campbell (see pages 21-22 of the office action dated 06/06/2006) are applicable to the new rejection set forth above.

Applicant argues that the references fail to teach the limitations of part (vi) of claim 1 and also fail to teach the limitation that the desired differentiate mammalian cell is from a transgenic non-human mammal (see page 14, paragraph 2 of Applicant's Remarks).

In response, both Zakhartchenko (1999) and Wells (1999) taught growing a first nuclear transfer embryo and using morulae from the first cloning round (see paragraph bridging pages 326-327 of Zakhartchenko and page 998, col. 2, paragraph 4 of Wells). Both Zakhartchenko and Wells each taught increased developmental capacity and cloning efficiency using a recloning step (see Zakhartchenko, page 326, col. 1, paragraph 2 and page 330, col. 1, paragraph 4; see also Wells, page 999, col. 2, paragraph 5). Zakhartchenko (2001) also taught the recloning step.

With respect to the newly added limitation requiring that the first donor cell, that in step (i) requiring that the donor cell come from a transgenic non-human mammal, Zakhartchenko (2001) taught use of a transgenic calves as a source of differentiated donor cells as set forth above.

3) The rejection of claim 16 under 35 U.S.C. 103(a) as being unpatentable over Schnieke (1997) as evidenced by Wilmut (1997, IDS), by Campbell (1996, IDS) and by Campbell (1994) in view of Zakhartchenko (1999, IDS) or Wells (1999, IDS) as previously applied to claims 1,2,5-9,11,13,17,19, 20, and 22, and further in view of Cibelli, (1998, IDS) is withdrawn in favor of the following new rejection necessitated by amendment to claim 1.

Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable over Schnieke (1997) as evidenced by Wilmut (1997, IDS), by Campbell (1996, IDS) and by Campbell (1994) in view of Zakhartchenko (1999, IDS) or Wells (1999, IDS) as applied to claims 1,2,5-9,11,13,17,19, 20,22,36 and 39 above, and further in view of Cibelli, (1998, IDS) and further in view of Zakhartchenko (2001).

As set forth above, Schnieke in view of Zakhartchenko (1999) or Wells taught a method of cloning a sheep using quiescent fetal fibroblast cells.

Schnieke did not teach use of non-quiescent cells as nuclear donors or use o f a transgenic mammal as a source of donor cells.

However, Cibelli taught use of non-quiescent fetal fibroblasts as nuclear donors to clone calves. Cibelli taught that active cell division is an indication of a relatively undifferentiated state (page 1256, col. 3, paragraph 1).

With respect to the newly added limitation requiring that the first donor cell, that in step (i) requiring that the donor cell come from a transgenic non-human mammal, Zakhartchenko (2001) taught use of a transgenic calves as a source of differentiated donor cells (page 363, col. 1, paragraph 4). Zakhartchenko also taught the caveats associated with transfection of donor cells in culture, providing motivation to use a known transgenic mammal as a donor rather than attempting to introduce a transgene de novo, to donor cells in vitro.

It would have been obvious at the time of filing to combine the methods of Schnieke and of Zakhartchenko (1999) or Wells and Zakhartchenko (2001) with the teachings of Cibelli using non-quiescent cells as nuclear donor. One of skill in the art at the time of filing would have been motivated to use a non-quiescent cell as a nuclear donor because Cibelli taught that other research had shown that the cell cycle stage of the donor cell affects the extent of development of an embryo after nuclear transfer (page 1256, col. 2, paragraph 2) and obtained a high efficiency of cloning using dividing cells. Furthermore, one would have been motivated use a transgenic mammal because such a mammal would

already have the transgene in the genome and characteristics of expression and function of the transgene would be known, avoiding the possibility of having a non-functional transgene in a resulting nuclear transfer mammal following transfection of non-transgenic donor cells in culture. Furthermore, Zakhartchenko taught that transfection of donor cells in culture had adverse effects on cloning efficiency (page 366, col. 2, paragraph 2-page 367). Thus, when available, one of skill in the art would be motivated to use a known, desired transgenic mammal as a source of donor cells rather than transfecting donor cells in culture.

One would have a reasonable expectation of success in combining the methods of Schnieke and of Zakhartchenko (1999) or Wells and Zakhartchenko (2001) (see above) with those of Cibelli because Cibelli demonstrated that dividing cells have the capacity to be reprogrammed to totipotency and are capable of generating a viable mammal. One would have a reasonable expectation of success in combining the above teachings because use of a transgenic mammal as opposed to a non-transgenic mammal does not alter the expectation of success and is further motivation for use of a transgenic mammal as a donor as Zakhartchenko (2001) taught the adverse effects of in vitro transfect of donor cells.

Thus, the claimed invention, as a whole, is clearly prima facie obvious in the absence of evidence to the contrary.

Applicant's arguments relating to the rejection of claim 16 under 35 U.S.C. 103(a) as being obvious over Schnieke et al. as evidenced by Wilmut, by Campbell and by Campbell, in view of Zakhartchenko (1999) and further in view of Cibelli (see pages 22-23 of the office action dated 06/06/2006) are applicable to the new rejection set forth above.

Applicant argues that the references fail to teach the limitations of part (vi) of claim 1 and also fail to teach the limitation that the desired differentiate mammalian cell is from a transgenic non-human mammal (see page 14, paragraph 2 of Applicant's Remarks).

In response, both Zakhartchenko (1999) and Wells (1999) taught growing a first nuclear transfer embryo and using morulae from the first cloning round (see paragraph bridging pages 326-327 of Zakhartchenko and page 998, col. 2, paragraph 4 of Wells). Both Zakhartchenko and Wells each taught increased developmental capacity and cloning efficiency using a recloning step (see Zakhartchenko, page 326, col. 1, paragraph 2 and page 330, col. 1, paragraph 4; see also Wells, page 999, col. 2, paragraph 5). Zakhartchenko (2001) also taught the recloning step.

With respect to the newly added limitation requiring that the first donor cell, that in step (i) requiring that the donor cell come from a transgenic non-human mammal, Zakhartchenko (2001) taught use of a transgenic calves as a source of differentiated donor cells as set forth above.

4) The rejection of claims 14,18 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schnieke (1997), as evidenced by Wilmut (1997, IDS), by Campbell (1996, IDS) and by Campbell (1994), in view of Zakhartchenko (1999, IDS) or Wells (1999, IDS) as applied to claims 1,2,5-9,11,13,17,19, 20 and 22 above, and further in view of DeSousa (US 6,548,741, published 12/06/2001 as US 2001/0049829) is withdrawn in favor of the following new rejection in light of Applicant's amendment to claim 1, requiring that the donor mammal be transgenic.

Claims 14,18 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schnieke (1997), as evidenced by Wilmut (1997, IDS), by Campbell (1996, IDS) and by Campbell (1994), in view of Zakhartchenko (1999, IDS) or Wells (1999, IDS) as applied to claims 1,2,5-9,11,13,17,19, 20,22,36 and 39 above, and further in view of DeSousa (US 6,548,741, published 12/06/2001 as US 2001/0049829) and further in view of Zakhartchenko (2001).

As set forth above, Schnieke taught a method of cloning a sheep using in vivo matured oocytes. Schnieke did not teach use of in vitro matured oocytes. Schnieke did not teach use of transgenic mammals as a source of donor cells.

However, DeSousa taught use of in vitro matured oocytes for nuclear transfer in pigs (col. 4, line 60-col. 5, line 4 and claim 1). DeSousa taught that the oocytes should be matured in vitro for about 42 to 46 hours prior to enucleation, which is within the claimed 10 to 60 hours as claimed (claim 18).

With respect to the newly added limitation requiring that the first donor cell, that in step (i) requiring that the donor cell come from a transgenic non-human mammal, Zakhartchenko (2001) taught use of a transgenic calves as a source of differentiated donor cells (page 363, col. 1, paragraph 4). Zakhartchenko also taught the caveats associated with transfection of donor cells in culture, providing motivation to use a known transgenic mammal as a donor rather than attempting to introduce a transgene de novo, to donor cells in vitro.

It would have been obvious for one of skill in the art at the time of filing to use in vitro matured oocytes as taught by DeSousa in the methods of Schnieke in combination with Zakhartchenko (1999) or Wells and Zakhartchenko (2001) (see above). One of skill in the art would have been motivated to substitute in vitro matured oocytes for in vivo matured oocytes because in vitro maturation would allow for harvesting of large numbers of immature oocytes from an ovary of a pig over hormonally inducing in vivo maturation and release of oocytes from pigs in vivo. In vitro maturation also allows for collection of oocytes post-mortem (see DeSousa, col. 9, lines 25-30). Furthermore, one would have been motivated use a transgenic mammal because such a mammal would already have the transgene in the genome and characteristics of expression and function of the transgene would be known, avoiding the possibility of having a non-functional transgene in a resulting nuclear transfer mammal following transfection of non-transgenic donor cells in culture. Furthermore, Zakhartchenko taught that transfection of donor cells in culture had adverse effects on cloning efficiency (page 366, col. 2, paragraph 2-page 367). Thus, when available, one of skill in the art would be motivated to use a known, desired transgenic mammal as a source of donor cells rather than transfecting donor cells in culture.

One would have a reasonable expectation of success in combining the methods of Schnieke with those of DeSousa because DeSousa demonstrated the success and capacity of in vitro matured oocytes to support parthenogenic activation to the same degree as in vivo-matured oocytes. One would have a reasonable expectation of success in combining the above teachings because use of a transgenic mammal as opposed to a non-transgenic mammal does not alter the expectation of success and is further motivation for use of a transgenic mammal as a donor as Zakhartchenko (2001) taught the adverse effects of in vitro transfect of donor cells.

Thus, the claimed invention, as a whole, is clearly prima facie obvious in the absence of evidence to the contrary.

Applicant's arguments relating to the rejection of claims 14 and 18 under 35 U.S.C. 103(a) as being obvious over Schnieke et al. as evidenced by Wilmut, by Campbell and by Campbell, in view of Zakhartchenko or Wells and further in view of DeSousa (see page 24 of the office action dated 06/06/2006) are applicable to the new rejection set forth above.

Applicant argues that the references fail to teach the limitations of part (vi) of claim 1 and also fail to teach the limitation that the desired differentiate mammalian cell is from a transgenic non-human mammal (see page 14, paragraph 2 of Applicant's Remarks).

In response, both Zakhartchenko (1999) and Wells (1999) taught growing a first nuclear transfer embryo and using morulae from the first cloning round (see paragraph bridging pages 326-327 of Zakhartchenko and page 998, col. 2, paragraph 4 of Wells). Both Zakhartchenko and Wells each taught increased developmental capacity and cloning efficiency using a recloning step (see Zakhartchenko, page 326, col. 1, paragraph 2 and page 330, col. 1, paragraph 4; see also Wells, page 999, col. 2, paragraph 5). Zakhartchenko (2001) also taught the recloning step.

With respect to the newly added limitation requiring that the first donor cell, that in step (i) requiring that the donor cell come from a transgenic non-human mammal, Zakhartchenko (2001) taught use of a transgenic calves as a source of differentiated donor cells as set forth above.

5) The rejection of claim 23 is rejected under 35 U.S.C. 103(a) as being unpatentable over Schnieke (1997) as evidenced by Wilmut (1997, IDS), by Campbell (1996, IDS) and by Campbell (1994), in view of Zakhartchenko (1999, IDS) or Wells (1999, IDS) as applied to claims 1,2,5-9,11,13,17 19, 20 22,36 and 39 above, and further in view of Park, (2001,IDS) is withdrawn in favor of the following new rejection in light of Applicant's amendment to claim 1, requiring that the donor mammal be transgenic.

Claim 23 is rejected under 35 U.S.C. 103(a) as being unpatentable over Schnieke (1997) as evidenced by Wilmut (1997, IDS), by Campbell (1996, IDS) and by Campbell (1994), in view of Zakhartchenko (1999, IDS) or Wells (1999, IDS) as applied to claims 1,2,5-9,11,13,17 19, 20 and 22 above, and further in view of Park, (2001,IDS) and further in view of Zakhartchenko (2001).

As set forth above under 35 USC 112, 2nd paragraph, claim 23 is unclear as to which step of the method requires omission of cytochalasin B from the method of introducing a donor nucleus into an enucleated oocyte.

As set forth above, Schnieke taught a method of cloning by nuclear transfer using cytochalasin B in the protocol. Schnieke did not teach cloning by nuclear transfer without use of cytochalasin B. Schnieke did not teach the use of a transgenic mammal as a source of donor cells.

However, Park et al taught that cytochalasin B is not necessary, and is contraindicated for methods of introducing a donor nucleus into a pig oocyte (paragraph bridging pages 1683-1684).

With respect to the newly added limitation requiring that the first donor cell, that in step (i) requiring that the donor cell come from a transgenic non-human mammal, Zakhartchenko (2001) taught use of a transgenic calves as a source of differentiated donor cells (page 363, col. 1, paragraph 4). Zakhartchenko also taught the caveats associated with transfection of donor cells in culture, providing motivation to use a known transgenic mammal as a donor rather than attempting to introduce a transgene de novo, to donor cells in vitro.

One of skill in the art would have been motivated to apply the teachings of Park to those of Schnieke in combination with Zakhartchenko (1999) or wells and Zakhartchenko (2001) and remove cytochalasin B from the activation protocol because Park taught that cytochalasin B is not necessary and can harm the integrity of the donor cells. One would have been motivated to remove cytochalasin B from the protocol because it is not necessary and to maintain donor cell integrity. Furthermore, one would have been motivated use a transgenic mammal because such a mammal would already have the transgene in the genome and characteristics of expression and function of the transgene would be known, avoiding the possibility of having a non-functional transgene in a resulting nuclear transfer mammal following transfection of non-transgenic donor cells in culture. Furthermore, Zakhartchenko taught that transfection of donor cells in culture had adverse effects on cloning efficiency (page 366, col. 2, paragraph 2-page 367). Thus, when available, one of skill in the art would be motivated to use a known, desired transgenic mammal as a source of donor cells rather than transfecting donor cells in culture.

One of skill in the art would have a reasonable expectation of success in combining the methods of Schnieke with those of Park because Park demonstrated that cytochalasin B is not necessary in manipulating donor cells and that removal does not inhibit the success of nuclear transfer. One would have a reasonable expectation of success in combining the above teachings because use of a transgenic mammal as opposed to a non-transgenic mammal does not alter the expectation of success and is further

motivation for use of a transgenic mammal as a donor as Zakhartchenko (2001) taught the adverse effects of in vitro transfect of donor cells.

Thus, the claimed invention, as a whole, is clearly prima facie obvious in the absence of evidence to the contrary.

Applicant's arguments relating to the rejection of claim 23 under 35 U.S.C. 103(a) as being obvious over Schnieke et al. as evidenced by Wilmut, by Campbell and by Campbell, in view of Zakhartchenko or Wells and further in view of Park (see pages 25-26 of the office action dated 06/06/2006) are applicable to the new rejection set forth above.

Applicant argues that the references fail to teach the limitations of part (vi) of claim 1 and also fail to teach the limitation that the desired differentiate mammalian cell is from a transgenic non-human mammal (see page 14, paragraph 2 of Applicant's Remarks).

In response, both Zakhartchenko (1999) and Wells (1999) taught growing a first nuclear transfer embryo and using morulae from the first cloning round (see paragraph bridging pages 326-327 of Zakhartchenko (1999) and page 998, col. 2, paragraph 4 of Wells). Both Zakhartchenko (1999) and Wells each taught increased developmental capacity and cloning efficiency using a recloning step (see Zakhartchenko, page 326, col. 1, paragraph 2 and page 330, col. 1, paragraph 4; see also Wells, page 999, col. 2, paragraph 5). Zakhartchenko (2001) also taught the recloning step.

With respect to the newly added limitation requiring that the first donor cell, that in step (i) requiring that the donor cell come from a transgenic non-human mammal, Zakhartchenko (2001) taught use of a transgenic calves as a source of differentiated donor cells as set forth above.

***Conclusion***

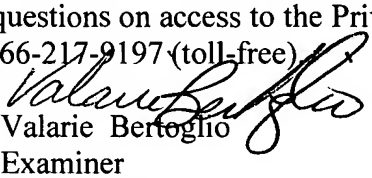
Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Valarie Bertoglio whose telephone number is (571) 272-0725. The examiner can normally be reached on Mon-Thurs 5:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Valarie Bertoglio
Examiner
Art Unit 1632